

**REMARKS**

Claims 1 through 16 and new Claim 17 are pending in the application.

Claim 1 has been amended to reflect advantageous embodiments in which B has been modified on the ring by an aza-substitution. Support for this amendment can be found in the Application-as-filed, for example on Page 7, lines 12 through 14.

Claim 1 has been further amended to reflect advantageous embodiments in which B has been optionally substituted with fluorine or methyl. Support for this amendment can be found in the Application-as-filed, for example on Page 5, lines 12 through 21.

Claim 12 has been amended to remove the term "dideoxyadenosine." Support for this amendment can be found in the Application as filed.

Claim 13 has been amended to remove the term "inosine." Support for this amendment can be found in the Application as filed.

Claim 17 has been added to complete the record for examination and highlight advantageous embodiments of the invention.

Claim 17 is directed to advantageous inventive processes in which the sulfide solution is at a temperature between 40 to 60 °C. Support for Claim 17 can be found in the Application-as-filed, for example on Page 7, lines 25 through 29.

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

Section 112 Rejection

Claims 1 through 15 stand rejected as indefinite over the recitation "modified." Applicants respectfully submit that one skilled in the art would readily be apprised of the scope of the foregoing term. Without further addressing the merits of the rejection and solely to advance prosecution of the above-referenced case, Claim 1 has been amended to reflect advantageous embodiments in which B has been modified on the ring by an aza-substitution. As noted above, support for this amendment can be found in the Application-as-filed, for example on Page 7, lines 12 through 14. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 1, 2, 10 and 11 stand rejected over recitation "optionally substituted." Applicants respectfully submit that one skilled in the art would readily be apprised of the scope of the foregoing term. Without further addressing the merits of the rejection and solely to advance prosecution of the above-referenced case, Claim 1 has been amended to reflect advantageous embodiments in which B has been optionally substituted with fluorine or methyl. As noted above, support for this amendment can be found in the Application-as-filed, for example on Page 5, lines 12 through 21. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 2, 9 and 16 stand rejected, as the Office Action urges that their chemical formulas do not correspond to 5'-(2-acetoxybutyryl)-2',3'-didehydro-2',3'-dideoxyinosine. Applicants respectfully submit that in Claim 2, P' can represent an acyl group RCO-, in which R represents a group R<sup>1</sup>COOC(R<sup>2</sup>R<sup>3</sup>)- and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> represent a C1-C6 alkyl. When R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are CH<sub>3</sub>, the compound 5'-(2-acetoxybutyryl)-2',3'-didehydro-2',3'-dideoxyinosine is encompassed. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Claim 12 stands rejected over the recitation "dideoxyadenosine." Without addressing the merits of the rejection, "dideoxyadenosine" has been deleted from Claim 12. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claim 13 stands rejected over the recitation "inosine." Without addressing the merits of the rejection, "inosine" has been deleted from Claim 13. Accordingly, Applicants respectfully request withdrawal of this rejection.

*The Claimed Invention is Patentable  
in Light of the Art of Record*

Claims 1 through 13, 15 and 16 stand rejected over United States Patent No. 5,466,793 to Honda et al in view of United States Patent No. 3,445,186 to Hrishikesan et al. Claim 14 stands rejected over the foregoing reference and further in light of WO 01/77103 to Bertolini et al.

It may be useful to consider the invention before addressing the merits of the rejection.

2',3'-didehydro-2',3'-dideoxynucleosides and 2',3'-dideoxynucleosides are known for their antitumoral and antiviral activity. 2',3'-dideoxynucleosides are generally prepared by the catalytic hydrogenation of 2',3'-didehydro-2',3'-dideoxynucleosides. One method by which the 2',3'-didehydro-2',3'-dideoxynucleosides can be prepared is via reductive elimination of 2',3'-dideoxy-2'(3')-(halo)-3'(2')-acylnucleosides with zinc and an activating agent.

Although useful for the formation of 2', 3'-didehydro-2',3'-dideoxynucleosides, zinc is known to poison any subsequent catalytic hydrogenation. Zinc may also present toxicological issues within medicaments. Unfortunately, heretofore known methods of removing zinc during 2',3'-didehydro-2',3'-dideoxynucleoside production have been of limited industrial applicability. Conventional methods of removing zinc during 2',3'-didehydro-2',3'-dideoxynucleoside production include use of ion-exchange resins or extraction by aqueous washing with chelating agents, such as EDTA, as evidenced by cited US 793. Unfortunately, such methods are particularly

Application No.: 10/567,696  
Filing Date: February 3, 2006  
Page No: 10

laborious and/or cannot be conveniently applied on a large scale. (In this regard, the Examiner's attention is kindly directed to the Application-as-filed on Page 2, line 19 through Page 3, line 14).

Surprisingly, Applicants have found highly advantageous methods of zinc removal from the reaction medium that are simple, efficient and easy to apply industrially, making the preparation of 2',3'-didehydro-2',3'-dideoxynucleosides very advantageous relative to the methods described in the literature. Altogether unexpectedly, zinc can be separated out of 2',3'-didehydro-2',3'-dideoxynucleoside as zinc sulfide. Specifically, a solution containing a polar solvent, preferably water, and alkali metal or alkaline-earth metal sulfides are added to an organic phase containing zinc, preferably the 2',3'-didehydro-2',3'-dideoxynucleoside reaction medium. The resulting precipitated zinc sulfate is then removed by standard techniques, for example centrifugation, decantation or filtration.

Accordingly, the claims are directed to processes for preparing 2',3'-didehydro-2',3'-dideoxynucleoside that include adding a sulfide solution of an alkali metal sulfide or alkaline-earth metal sulfide to precipitate divalent zinc as zinc sulfide from the organic phase.

Applicants respectfully submit that the cited references do not teach or suggest the claimed invention.

Honda is merely directed to conventional methods by which to form 2',3'-dideoxyinosine. Honda teaches the removal of zinc via a number of conventional methods, including ion exchange resins and chelating agents. (Col. 7, lines 15 – 25). Honda goes no to enumerate a number of suitable chelating agents, including aminocarboxylic acids, phosphates and hydroxycarboxylic acids. (Col. 7, lines 26 – 35). Although specifying a number of suitable chelating agents, Honda does not provide suitable temperatures for their use.

Application No.: 10/567,696  
Filing Date: February 3, 2006  
Page No: 11

Honda, merely evidencing conventional processes for zinc removal, thus does not teach or suggest the inventive processes for preparing 2',3'-didehydro-2',3'-dideoxynucleosides comprising adding a sulfide solution of an alkali metal sulfide or alkaline-earth metal sulfide to precipitate divalent zinc as zinc sulfide from the organic phase, as correctly noted by the Examiner.

And Honda most certainly does not teach or suggest the addition of such sulfide solution at a temperature between 40 to 60 °C, as recited in Claim 17.

Accordingly, Applicants respectfully submit that Honda does not teach or suggest the claimed invention, considered either alone or in combination with the remaining art of record.

Hrishikesan does not cure the deficiencies in Honda.

Hrishikesan is directed to methods of producing aluminous ore. Hrishikesan is particularly directed to the use of insoluble bauxite residues to entrap ore contaminants. (Col. 2, lines 25 – 30). Hrishikesan's solution, at temperatures of up to 220 °F, is added to an unclarified bauxite slurry, and the resulting precipitate is then trapped within insoluble bauxite residues. (Col. 2, lines 55 – 60 and Col. 4, lines 32 - 34). Applicants respectfully submit that zinc sulfide is colloidal in nature and, as a consequence, it is difficult to separate from the aluminate solution.

Hrishikesan, directed to aluminous ore and requiring bauxite residues to absorb contaminant, does not teach or suggest the inventive processes for preparing 2',3'-didehydro-2',3'-dideoxynucleosides, much less such processes comprising adding a sulfide solution of an alkali metal sulfide or alkaline-earth metal sulfide to precipitate divalent zinc as zinc sulfide from the organic phase. In fact, Applicants respectfully submit that to modify Hrishikesan so as to avoid its required bauxite, particularly the required insoluble bauxite residues, would render it unfit for its intended purpose.

And Hrishikesan, teaching temperatures of up to 220 °F, most certainly does not teach or suggest the addition of such sulfide solution at a temperature between 40 to 60 °C, as recited in Claim 17.

Accordingly, Applicants respectfully submit that Hrishikesan likewise fails to teach or suggest the claimed invention.

Applicants further respectfully submit that there would have been no motivation to have combined these references.

Honda is directed to conventional methods by which to form 2',3'-dideoxyinosine. Hrishikesan is directed to methods of producing aluminous ore that use insoluble bauxite to trap contaminants. These are altogether different fields of endeavor and problems solved, to say the least.

However, even if combined (which Applicants did not), the claimed invention would not result.

The combination particularly does not teach or suggest the inventive processes for preparing 2',3'-didehydro-2',3'-dideoxynucleosides comprising adding a sulfide solution of an alkali metal sulfide or alkaline-earth metal sulfide to precipitate divalent zinc as zinc sulfide from the organic phase.

And the combination most certainly does not teach or suggest the addition of such sulfide solution at a temperature between 40 to 60 °C, as recited in Claim 17.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of Honda and Hrishikesan, considered either alone or in combination.

Application No.: 10/567,696  
Filing Date: February 3, 2006  
Page No: 13

Claim 14 is likewise patentable in light of the foregoing references and further in light of Bertolini.

Bertolini is directed to methods by which to produce 2', 3'-didehydro-3'-deoxythymidine using particular activating agents. (Page 1, first paragraph and Page 2, first full paragraph).

Applicants respectfully submit that there likewise would have been no motivation to have combined these references.

Honda is directed to conventional methods by which to form 2',3'-dideoxyinosine. Bertolini is directed to methods by which to produce 2', 3'-didehydro-3'-deoxythymidine using particular activating agents. Hrishikesan is directed to methods of producing aluminous ore that use insoluble bauxite to trap contaminants. These are altogether different fields of endeavor and problems solved, to say the least.

However, even if combined (which Applicants did not), the claimed invention would not result.

The combination more particularly does not teach or suggest the inventive processes for preparing 2',3'-didehydro-2',3'-dideoxynucleosides comprising adding a sulfide solution of an alkali metal sulfide or alkaline-earth metal sulfide to precipitate divalent zinc as zinc sulfide from the organic phase, as recited in Claim 14.

Accordingly, Applicants respectfully submit that Claim 14 is likewise patentable in light of Honda, Hrishikesan, and Bertolini, considered either alone or in combination.

Application No.: 10/567,696  
Filing Date: February 3, 2006  
Page No: 14

**CONCLUSION**

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 17 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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